# CAPSULES, SOFT

**David H. Bergstrom**
**R.P. Waranis**
**M.S. Rahman**
*Cardinal Health Pharmaceutical Technologies & Services Center, Somerset, New Jersey, U.S.A.*

**J.C. Ferdinando**
*R.P. Scherer Limited, Swindon, United Kingdom*

## INTRODUCTION

Soft gelatin capsules (also referred to as soft elastic gelatin capsules, Liqui-gels®, or softgels) are a unique drug delivery system that can provide distinct advantages over traditional dosage forms such as tablets, hard-shell capsules, and liquids. However, due to economic, technological, and patent constraints, there are relatively few manufacturers of softgels in the world (1).

Some of the major advantages of softgels include:

- improved bioavailability (increased drug absorption (2))
- speed of product development
- enhanced drug stability (protection against oxidation, photodegradation, and hydrolysis in lipophilic systems)
- superior patient compliance/consumer preference (ease of swallowing, appealing appearance, absence of objectionable taste, and convenience) and pharmaceutical elegance
- excellent dose uniformity (less than $\pm 1\%$ for solution fills; $\pm 1-3\%$ for suspension fills)
- better tamper evidence (tampering leads to puncturing and visible leakage)
- safer handling of highly potent or cytotoxic drug compounds
- product differentiation (through selection of novel shapes, colors, and sizes)
- excellent product life-cycle management.

In comparison, the disadvantages of softgels are relatively few. These include:

- specialized manufacturing equipment requirements
- higher cost for manufacturing as compared to tablets
- limited availability of technical experts

In surveys comparing various pharmaceutical dosage forms, softgels are rated as a high tech dosage form with strong customer preference. They are formed, filled, and sealed in a single operation. Once production for a specific product begins, the manufacturing process normally proceeds 24 h per day until the lot of product is completed. This results in a manufacturing environment that operates around the clock, 7 days a week.

The standard softgel shapes for oral pharmaceutical products are oval, oblong, and round, though softgels can be easily manufactured in any shape. A recent survey has shown that smaller sized softgels are preferred within each shape category, with oval being the most popular shape.

## DESCRIPTION

The softgel (Fig. 1) is a hermetically-sealed, one-piece capsule with a liquid or semisolid fill. The softgel consists of two major components, the gelatin shell and the fill (Fig. 2). In the finished product, the gelatin shell is primarily composed of gelatin, plasticizer, and water. The fill materials can include a wide variety of vehicles and can be either a solution or a suspension. Softgels may be coated with suitable enteric coating agents, such as cellulose acetate phthalate, to obtain enteric release of encapsulated material.

Because of their special properties and advantages, softgels are used extensively in many pharmaceutical, cosmetic, and nutritional products. The primary pharmaceutical applications include oral dosage forms, chewable softgels, suppositories, and topical products. The size of a softgel represents its nominal capacity in minims (1 cc = 16.23 minims). For example, an 11 oblong softgel can be filled with 8.5–11.0 minims of fill formulation.

## FORMULATION DEVELOPMENT

Having selected the softgel dosage formulation of a drug, the desired performance characteristics will influence the

**Fig. 1** Examples of softgels.

nature of the development of that formulation. The first consideration in this process is whether the softgel should be transparent, containing a solution of drug, or opaque, containing a drug suspension. Next, it must be determined whether the formulation is intended to provide bioequivalence with another product or to have enhanced performance in vivo; for example, faster or more complete absorption. This section will discuss the formulation principles of softgels, including gelatin shell and fill formulations.

## Gelatin Shell Formulation

Typical softgel shells consist of gelatin, plasticizer, water, and materials that impart the desired appearance (colorants and/or opacifiers) and, on occasion, flavors and/or preservatives. A description of the functions, types, and amounts of materials most often used in manufacturing softgel shell formulations is detailed in the following paragraphs.

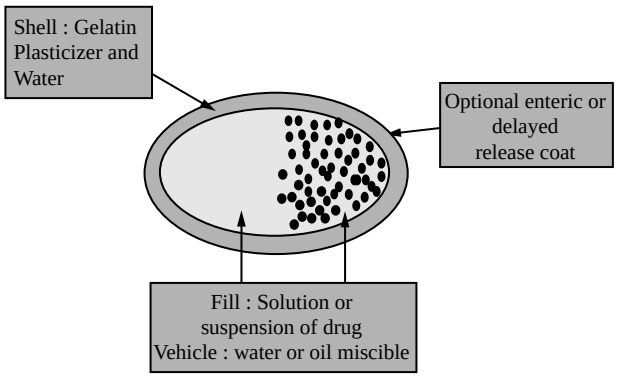


**Fig. 2** Softgel components.

### Gelatin

Gelatin provides the structural support for the shell of the softgel. It is typically 40–50% of the wet gel formulation and can be either Type A (acid processed) or Type B (alkali processed). The selection for the type of gelatin for a particular softgel formulation is based on compatibility with the other ingredients (both active and inactive) within the softgel. The steps involved in the gelatin manufacturing process include extraction, neutralization, drying, and grinding (3). The physicochemical properties of gelatin are largely controlled by the source of collagen, extraction method, pH, thermal history, and electrolyte content.

### Plasticizers

Plasticizers are used to make the softgel shell elastic and pliable. The ratio of plasticizer to gelatin determines the hardness of the shell, assuming there is no effect from the fill. Plasticizers generally account for 20–30% of the wet gel formulation and are commonly glycerin, sorbitol, or propylene glycol, either individually or in combination. Several proprietary blends of sugar mixtures with sorbitol anhydrides can also be used and are available from excipient suppliers (4, 5). The amount and choice of the plasticizer help to determine the hardness of the final product, and may also affect the dissolution or disintegration of the softgel, as well as its physical and chemical stability. Plasticizers are selected on the basis of their compatibility with the fill formulation, processing (drying) time, and desired properties of the final softgels, including hardness, appearance, handling characteristics, stability, and even the geographical location in which the product will be sold.

### Water

Water usually accounts for 30–40% of the wet gel formulation and is critical to ensure proper processing during gel preparation and softgel encapsulation. Following encapsulation, excess water is removed from the softgels through controlled drying, leaving the equilibrium water content typically at less than 10%.

### Colorants/Opacifiers

Colorants and opacifiers are typically used at low concentrations in the wet gel formulation. A wide range of colorants such as FD&C and D&C water-soluble dyes, certified lakes, pigments, and vegetable colors have been incorporated into gelatin shells alone or in combination to produce the desired color, tint, or hue for product identification. A general rule in color selection is that the color of the capsule shell should be similar to or darker than the fill material.

An opacifier is sometimes added to the gelatin shell to obtain an opaque shell for suspension fills or to protect light sensitive fill ingredients. Titanium dioxide is the most commonly used opacifier. Flavors such as ethyl vanillin and essential oils are sometimes included in the capsule shell to impart desirable odors or flavors or to offset odoriferous materials that may be contained within the softgel itself.

### Fill Formulation

Because of the migration of components (water, plasticizers, drugs, etc.) within the softgel both during and following encapsulation, formulation of the fill material must be conducted concurrently with formulation of the shell for maximum product quality. Without this simultaneous development, it is not uncommon for problems to arise.

The viscosity of fills can range from mobile liquids to thick suspensions or pastes. The fill material in a soft gelatin capsule can be a liquid, a combination of miscible liquids, a solution of a solid(s) in a liquid(s), or a suspension. These formulations are designed to produce the smallest possible capsule consistent with acceptable chemical and physical stability, therapeutic effectiveness, and production efficiency.

The large groups of liquids that can be encapsulated into softgels fall into one of two categories: water-miscible liquids and water-immiscible liquids (6).

Water-miscible liquids include polyethylene glycols and nonionic surfactants, such as the polysorbates. Low molecular weight grades of polyethylene glycol (e.g., PEG 400) are used most commonly since they remain liquid at ambient temperatures. Small amounts (up to 5–10%) of other water-miscible liquids, such as propylene glycol, ethanol, and glycerin, can also be used.

Water-immiscible liquids include vegetable and aromatic oils, aliphatic, aromatic and chlorinated hydrocarbons, ethers, esters, high molecular weight organic acids, and some alcohols.

Liquids that are likely to cause problems following encapsulation are low molecular weight water-soluble and volatile organic compounds, such as some alcohols, acids, ketones, and esters; water (above 5%); emulsions (whether oil in water or water in oil); liquids with extremes of pH; and aldehydes.

Drugs that are not sufficiently soluble in the solvent or combinations of solvents can be formulated into suspensions and encapsulated. The particle size of insoluble drugs should be 80 mesh or finer for maximum suspension homogeneity and capsulation equipment requirements. Examples of suspending agents include paraffin wax, beeswax, and hydrogenated vegetable oil for oily vehicles, and solid glycol esters (such as higher molecular weight PEG) for nonoily vehicles. Surfactants, such as polysorbates, are often added to the dispersion to promote wetting of the ingredients and/or dispersion of the fill in vivo.

In general, many different materials may be encapsulated; however, limitations do exist for some compounds due to high solubility in water and/or inherent chemical reactivity and the resultant effect on the shell. These compounds include strong acids and alkalis and their salts, as well as ammonium salts. Some compounds, such as aldehydes, can react with gelatin, causing crosslinking and resulting in a product that lacks bioavailability. In addition, any substance (such as aspirin) that is unstable in the presence of moisture may also exhibit unacceptable chemical stability in softgels.

## PRODUCT DEVELOPMENT

This section will discuss the rationale of softgel product development, including solubility screening, gel compatibility, process development, and trial batch manufacture, concluding with a review of the manufacturing process and specialized formulation approaches to enhance pharmacokinetic performance.

The flow diagram in (Fig. 3) details the activities normally undertaken in the development of a softgel. The major steps involved are described in the following paragraphs.

The first step in developing a solution containing softgel is to determine the solubility of the drug in a range of pharmaceutically acceptable solvents. After the solubilities are measured, the solvents are then selected on the basis of their regulatory acceptability and known compatibility with softgel dosage forms. The types of excipient typically include:

- hydrophilic solvents
- lipophilic materials
- hydrophilic surfactants
- lipophilic surfactant
- co-solvents.

Solvents that provide adequate solubility of the drug can be selected, though it may be necessary to combine them to achieve the desired in vitro or in vivo characteristics and to ensure good physical stability. In addition to characterizing the in vitro and in vivo performance of the preliminary formulation, it is important to evaluate the drug solubility in the mixtures for the following conditions:

- physical stability under accelerated conditions
- chemical stability under accelerated conditions
- excipient compatibility.

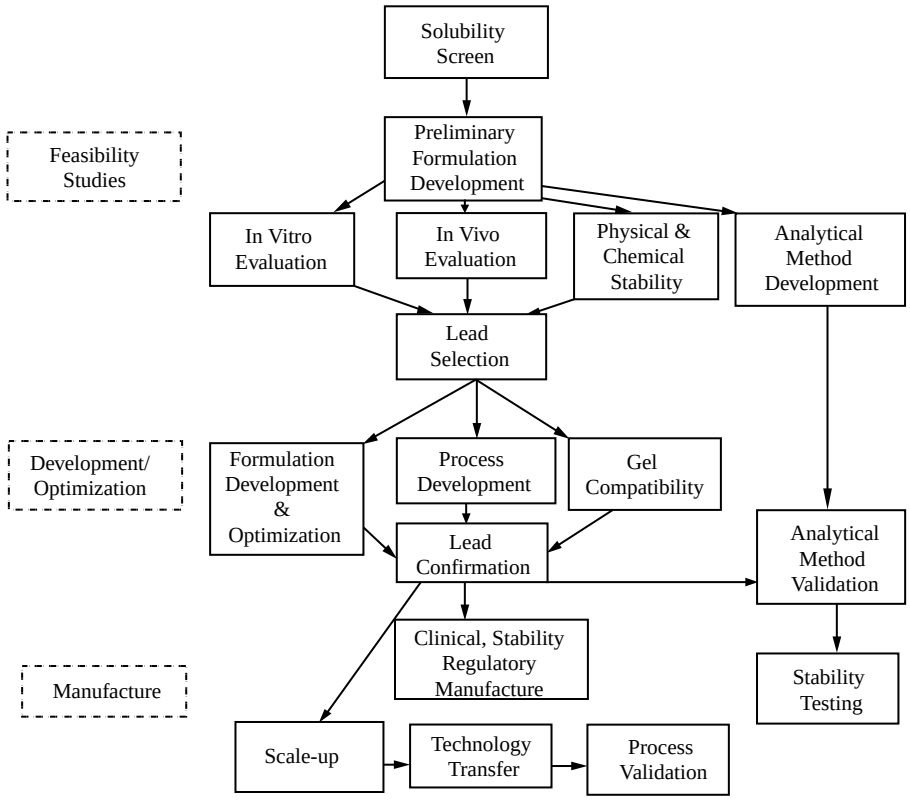


**Fig. 3** Typical softgel development flow diagram.

For softgels containing suspension fills, the solubility of the drug in a range of pharmaceutically acceptable solvents is also measured and excipients in which the drug shows little or no solubility are then selected. These formulations generally require viscosity enhancers in order to provide adequate suspending characteristics for the drug during processing. This is vital in maintaining drug homogeneity during manufacture. The type and level of viscosity enhancer is optimized to provide the best manufacturability.

### Gel Compatibility

Thorough gel compatibility testing between the fill and shell formulation is an important part of the development process. A variety of problems may result if the fill is not well matched to the proper shell formulation. These may be observed either immediately after encapsulation or after prolonged storage.

### Process Development/Trial Manufacture

Having identified potential fill and shell formulations on the laboratory scale, a suitable manufacturing process that will enable successful preparation of the trial batch materials required for regulatory and clinical studies must be developed. Such process development includes investigating several processing parameters, such as the order of addition, temperature, mixing condition, and selection of equipment.

Formulations selected for stability and clinical evaluation will be prepared as trial (pilot) batches. During manufacture, the process and product will be evaluated to provide valuable information for later process ranging and validation studies. For example, the fill moisture and hardness of the capsules during the drying stages will be monitored to optimize the drying process and resulting product stability. Fig. 4 shows the drying profile of a softgel product. Note that the reduction in fill moisture is accompanied by an increase in capsule hardness.

## METHOD OF MANUFACTURE

As early as the 1830s, softgels were used as a method of drug delivery. Early manufacturing included both a hand-dipping method and a plate-press method. The hand-dipping

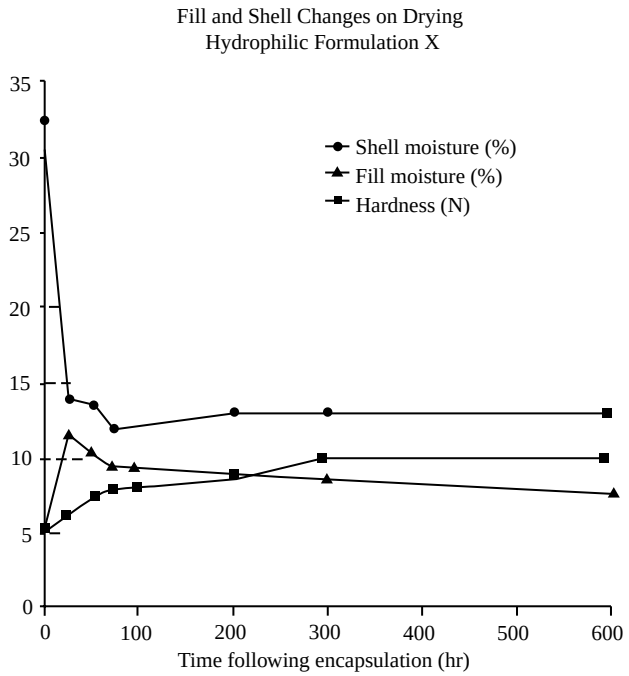


**Fig. 4** Typical drying profile.

method created individual empty softgel shells that were subsequently filled with a syringe or dropper. The plate-press method was a batch process that involved pressing two sheets of wet gelatin together between two molds. The molds provided depressions in the gelatin sheet into which active fill was then placed. A second gelatin sheet was laid over the first and both were pressed together with fill material sandwiched between. The pressure of the plate dies sealed the top and bottom sheets of gelatin together and cut out the individual softgels for subsequent drying.

Almost every softgel on the market today is made using the rotary die process patented by Scherer in 1933 (7). The equipment and manufacturing process has improved dramatically over the years, but the underlying manufacturing principle remains essentially unchanged. In this method, two independent processes take place, often simultaneously, yielding two different materials, the gel mass and the fill material. Both are united in the encapsulation process that produces wet softgels.

The wet gel mass is manufactured by mixing together and melting, under vacuum, the gelatin shell ingredients (gelatin, plasticizer, water, colorants and sometimes opacifiers, flavors, and preservatives). At the encapsulation machine (Fig. 5), molten gel mass flows through heated transfer tubes and is cast onto chilled drums, forming two separate ribbons, each approximately 6 in. wide. The thickness of the ribbons (usually 0.02–0.04 in.) is carefully controlled and checked periodically throughout manufacture. The gel ribbons traverse through rollers that provide proper alignment of the ribbons and apply lubricant to both surfaces of the ribbons. Each gel ribbon forms one half of the softgel. Two-toned softgels are made using two different colored gel ribbons.

Active fill materials are manufactured in a process separate from the gel mass manufacture. The viscosity of

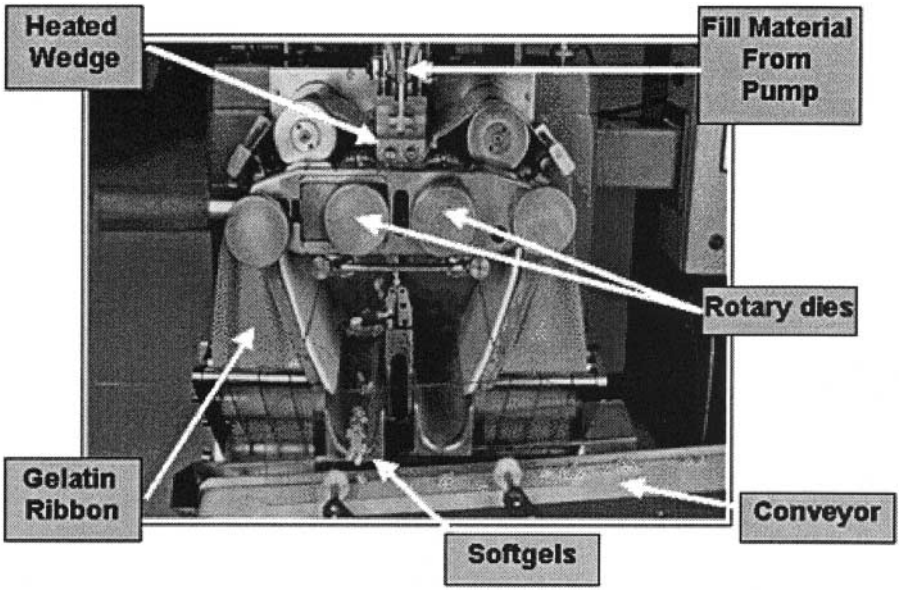


**Fig. 5** Encapsulation equipment.

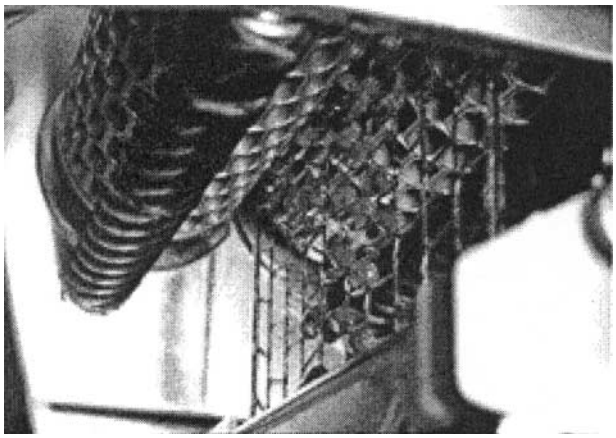

**Fig. 6** Newly formed softgels.

all fills and the particle size of suspended materials are important parameters established during development and controlled throughout manufacture.

Softgels are formed during the encapsulation part of the process, using the two gel ribbons and the fill material. Lubricated gel ribbons are fed between a pair of counter-rotating dies, the surface of which contains matching pockets of appropriate size and shape that serve as molds for forming the softgels. The die pockets also seal both sides of the softgel and cut the formed softgel away from the residual gel ribbon. Fig. 6 shows softgels immediately following encapsulation as they are being separated from the ribbons. The softgels are then conveyed to a tumble dryer to initiate drying.

Situated between the ribbons and rotating dies is the wedge as shown in Figs. 7 and 8. The wedge serves three separate functions during the encapsulation process. First, it heats the gel ribbons close to the gel–sol transition temperature to ensure that melting (welding) of the two gel ribbons occurs when the ribbons are pressed together between the dies. Second, the wedge is part of the system that distributes the fill material from a positive displacement pump to each of the die pockets. Finally, the wedge, in conjunction with the lubricant, provides a sealing surface against the ribbons to eliminate air and allows a seal to be formed between the shell and fill material without the introduction of air into the product.

In order to properly manufacture the gel mass and form the gel ribbons, the gel mass formulation contains excess water. Following encapsulation, softgels must be dried to obtain a final product that will be durable enough to withstand subsequent processing, packaging, and shipping, and possess good long term physical stability. Drying occurs in two stages. Initial drying takes place in a rotating basket dryer that tumbles the softgels in temperature and humidity controlled air. This removes approximately half of the excess water. The balance of the excess water is removed during the secondary drying stage, when the softgels are spread in a single layer on shallow trays. The trays are designed and stacked to allow air to pass through the rack and around the softgels (Fig. 9). Secondary drying proceeds under controlled conditions of temperature and humidity until the appropriate level of hardness or fill moisture is achieved. Complete drying can

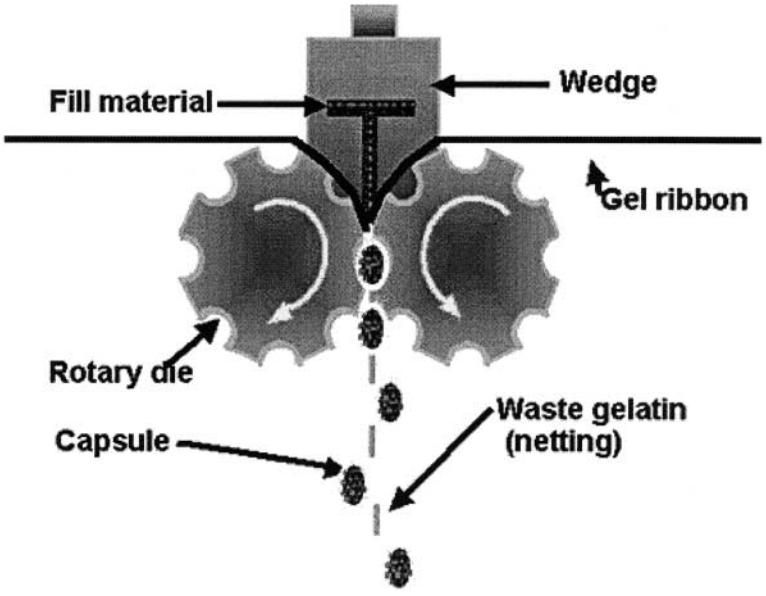


**Fig. 7** Softgel encapsulation process.

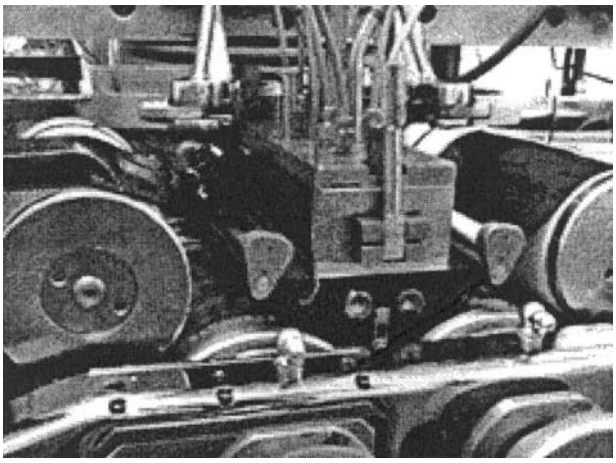

**Fig. 8** Close-up of die-wedge equipment.

take from 3 days to 3 weeks depending on shell and fill formulations and the size of the softgel.

Once the softgels have reached the desired drying endpoint, they are placed into bulk holding containers to prevent further drying. At this point, several additional operations may be performed, including washing, printing, inspecting, and packaging.

## THERAPEUTIC PERFORMANCE

The pharmacokinetic performance of drugs can be enhanced by softgel dosage forms, the exact formulation of which depends on the desired pharmacokinetic improvement. The two most common requirements for this formulation are faster and more complete absorption. In both cases, the ideal situation is for the drug to be dosed in solution and formulated to remain in solution after dispersion in gastrointestinal media, possibly as a nanoemulsion. Formulation of nanoemulsion preconcentrates for softgel encapsulation requires the drug to be in solution in a mixture of oils, surfactants, cosurfactants, and possibly cosolvents.

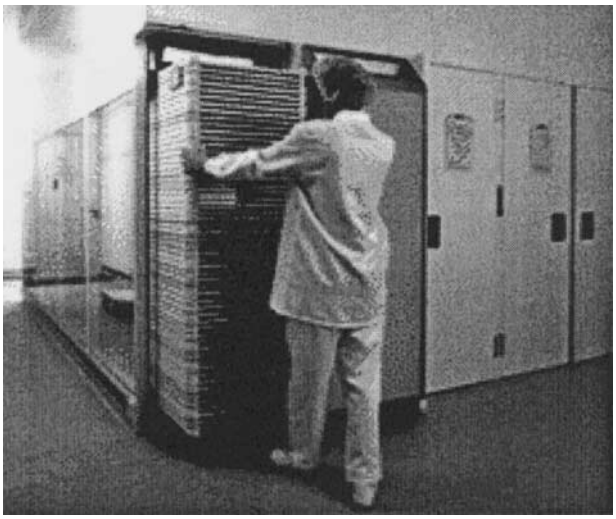

**Fig. 9** Tray drying of softgels in controlled drying tunnels.

### Rate of Absorption

Noteworthy advances recently have been made in the development of softgel formulations to address particular performance issues in vivo. These include presentation of the drug to the gastrointestinal tract in a solution from which the drug can be absorbed significantly faster than that from a solid oral dosage form, which may be rate-limited by the need for disintegration followed by drug dissolution. With the solution–softgel approach, the shell ruptures within minutes to release the drug solution, usually in a hydrophilic or highly dispersing vehicle that aids the rate of absorption. This can be a valuable attribute for treatments such as migraine or acute pain, or where there is a limited absorption window in the gastrointestinal tract. Fig. 10 compares the absorption rates between a solution softgel formulation and a tablet of ibuprofen (8). The data are based on a pharmacokinetic comparison of 400 mg ibuprofen in 12 human volunteers.

### Increased Bioavailability

In addition to increasing the rate of absorption, softgels may also improve the extent of absorption. This can be particularly effective for large hydrophobic drugs.

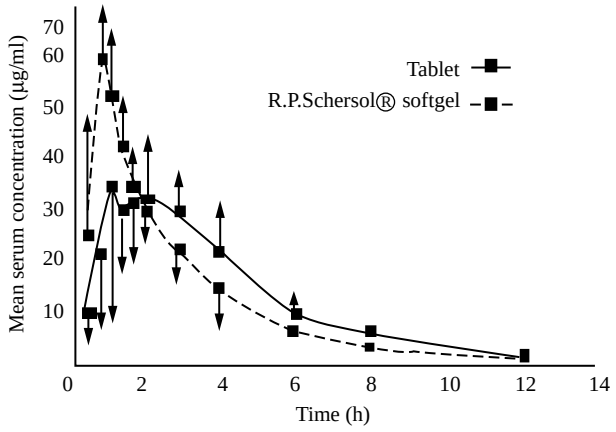


**Fig. 10** Comparison of absorption rates of ibuprofen from softgel and tablet.

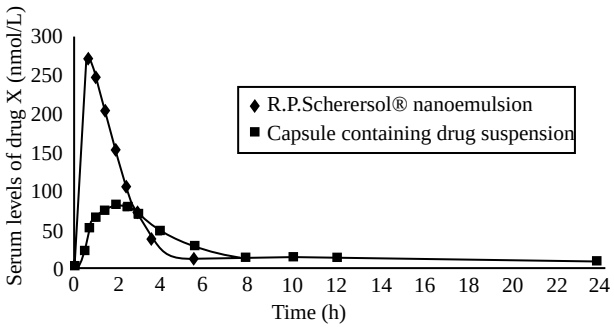


**Fig. 11** Comparison of nanoemulsion softgel to a drug suspension capsule.

Recently, the protease inhibitor saquinavir has been relaunched in a patented solution–softgel formulation, providing approximately three times the bioavailability as the original hard-shell formulation (9).

In some cases, drugs may be solubilized in vehicles capable of spontaneously producing a microemulsion or nanoemulsion on contact with gastrointestinal fluids. This particular vehicle consists of oils and surfactants in appropriate proportions which, on contact with aqueous fluids, produce an emulsion preferably with an average droplet size less than 100 nm. The solubility of the drug should be maintained as long as possible, delivering solubilized drug directly to the enterocyte membrane. It may even be possible to utilize the body's own systems for oil digestion to produce micelles containing solubilized drug. Fig. 11 depicts the enhancement in plasma levels achieved in 12 human volunteers when a nanoemulsion softgel was used to dose a hydrophobic drug as compared to a capsule containing a suspension of micronized drug particles (9).

### Decreased Plasma Variability

High variability in drug plasma levels is a common characteristic of drugs with limited bioavailability. By dosing the drug optimally in solution, the variability of such drug plasma levels can often be reduced. Cyclosporin benefits from such an approach (10). Fig. 12 depicts the administration of a 10 mg/kg dose of Cyclosporin A (Sandimmune®) softgel solution formulation in eight human volunteers (11). Fig. 13 depicts the administration of a 10 mg/kg dose of Cyclosporin A (Neoral®) microemulsion preconcentrate softgel formulation in eight fasting human volunteers (11).

## PRODUCT QUALITY CONSIDERATIONS

### Ingredient Specifications

Numerous specifications and control measures are employed to determine final product quality, the first of which is ensuring adequate quality of excipients and active ingredients. Excipient testing ensures compliance with compendial specifications, as well as specifications determined during development of the fill material and/or shell formulation. Among these are limiting values for trace impurities, especially peroxides, aldehydes, some metals, and ionic salts. Presence of these impurities can result in gelatin crosslinking and possible dissolution

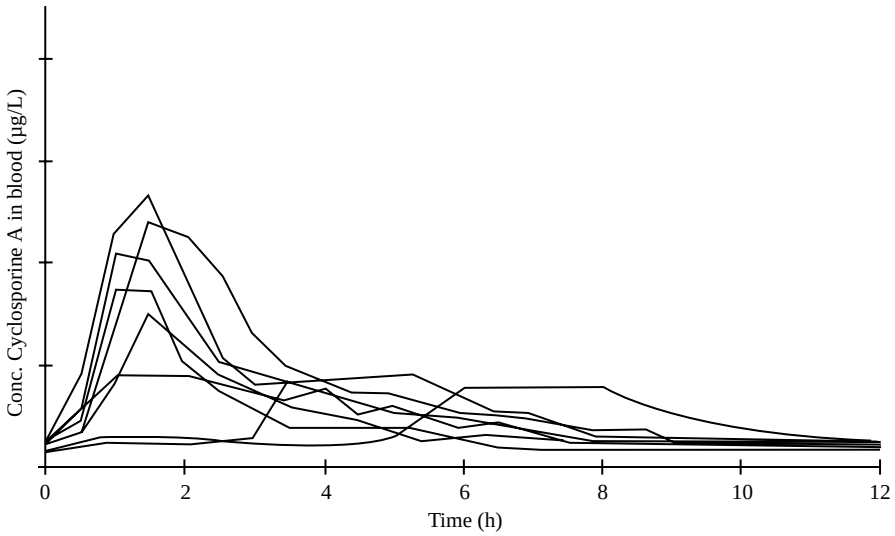


**Fig. 12** Cyclosporine A (Sandimmune®) softgel formulation.

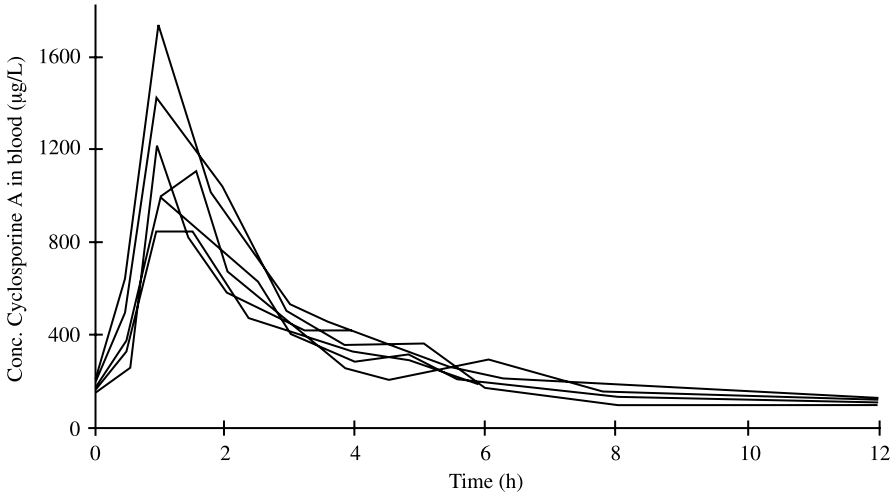


**Fig. 13** Cyclosporine A (Neoral®) microemulsion preconcentrate softgel formulation.

problems or in undesired changes in the product appearance over time.

Since gelatin is the key ingredient for the shell and is present in larger quantities than other excipients, it is important to ensure that the gelatin meets not only current USP specifications, but the additional controls of particle size, viscosity, and bloom strength, all of which are significant for manufacturing process as well as final product stability. Other specifications, such as the quantity of certain ionic materials, are necessary to ensure stable product appearance during storage. Furthermore, it is essential to specify or limit other gelatin properties, such as color or even the source of the gelatin (bovine, porcine, bone, hide), depending on the formulation and intended market of the final product.

### In-Process Testing

Several tests are conducted on a regular basis throughout the encapsulation portion of the softgel manufacturing process. These include weight determinations for both the fill material and the shell, and measurements of the thickness of the seals of the softgels themselves.

Fill moisture and/or hardness measurements are performed during the drying process, the results of which are used to determine the drying endpoint for each lot. Specifications for fill weight, shell weight, seam thickness, and drying endpoints are based on the softgel size, amount and type of fill, and the results obtained during previous process development studies.

### Final Product Testing

Once the softgels have completed all required processing steps, the lot is inspected and sampled for final product release testing. Tests required for final product release are dependent on regulatory requirements for the product and usually include microbiological testing, assay and identity of actives, physical appearance, fill weight, dissolution or disintegration, and dosage uniformity.

## RECENT ADVANCES IN NEW TECHNOLOGY

Recent advances in the development of softgel formulations and manufacturing have lead to exciting improvements, including the capability of imprinting the product logo directly on the wet gelatin ribbon prior to encapsulation, the ability to encapsulate small quantities of softgels in the laboratory setting for early stability or quick in vivo evaluations, and the ability to encapsulate microspheres (controlled or immediate release) suspended in the fill.

## TRENDS IN PATENT ACTIVITY

A review of the United States patent activity over the past decade reveals some interesting trends within the softgel technology arena. While the review is limited to U.S. patents, it most likely represents the patent activity on a worldwide basis. A listing of the more significant patents, sorted into groups relating to either formulations (12–21), manufacturing technology (22–29) or softgel design innovations (30–40), has been included in the reference section.

In 1990, there were 210 patents issued citing soft gelatin capsules as either specific claims or examples of

possible dosage forms. Over the past 12 months, approximately 760 patents were issued. Pharmaceutical application of soft gelatin capsule technology has increased over the past decade. This fourfold increase in the number of patents involving softgels may suggest a broader understanding of the benefits of this technology both in clinical performance as well as patient and consumer appeal.

Looking more closely at patents over the same period, there were 45 U.S. patents issued in 1990 where the soft gelatin capsule was a specific claim. The past 12 months yielded approximately 300 patents with softgels as a specific claim. This analysis is probably a better indication of patent activity specifically related to the softgel technology. This sixfold increase in the number of patents specifically involving softgel formulations may reflect greater and more widespread expertise with regard to softgel formulation processes. It may also be an indication of the greater proportion of "difficult" to formulate drugs currently coming out of basic research centers, that is, low aqueous solubility and/or poor or variable gastrointestinal absorption.

Examination of the patent activity of the top 20 pharmaceutical companies, or their predecessor companies, in the year 2000 vs. 1990 suggests an industry sector shift in the use of soft gelatin capsules. In 1990, the top 20 pharmaceutical firms obtained 85% of patents. This decreased to 57% over the past 12 months. Since overall pharmaceutical application of softgel technology has increased, a reasonable inference would be that the comparatively young and smaller biopharmaceutical industry sector is coming of age as compounds begin to move from basic research to development and commercialization.

Over the 1990 and 2000 periods, 95% of patents granted for pharmaceutical softgel products relate to drugs or fill formulations and not to specific claims or improvements regarding shell formulations or manufacturing processes. On the surface, this would appear to indicate a mature technology but since patents are public domain and process patents are difficult to enforce it is more likely that industry leaders are reluctant to pursue patents except in unusual circumstances. In this process-critical industry it is more reasonable to expect that companies prefer to maintain technological advances as internal know-how for competitive reasons.

## CONCLUSION

Despite the specialized manufacturing process, softgels provide a versatile and efficient drug delivery system with distinct advantages over conventional dosage forms, including improved bioavailability, shorter development times, superior patient preference, and enhanced dose uniformity. The inherent nature of the softgel offers a wide variety of usage and fill options. In any softgel product development effort, formulation of the fill and gelatin shell should be considered concurrently in order to optimize product quality and performance.

## REFERENCES


1. Stanley, J.P. Soft Gelatin Capsules. *The Theory and Practice of Industrial Pharmacy*, 2nd Ed.; Lachman, L., Lieberman, H.A., Kanig, J.L., Eds.; Lea Febiger: Philadelphia, 1976; 359.
2. Ferdinando, J.C. Formulation Solutions—Softgels. Pharmaceutical Manufacturing and Packaging **2000**, March, 69–73.
3. Ward, A.G.; Courts, A. *The Science and Technology of Gelatin*; Academic Press: New York, 1977.
4. SPI Polyols, Inc. 321 Cherry Lane New Castle, DE 19720.
5. Rouquette America, Inc., Corporate Headquarters: 1417 Exchange Street, P. O. Box 6647 Keokuk, IA 52632-6647.
6. Jimerson, R.F. Softgel (Soft Gelatin Capsule) Update. Drug Development and Industrial Pharmacy **1986**, *12* (8/9), 1133–1137.
7. Scherer, R.P. US Patent 1,970,396, 1934.
8. Saano, V.; Paronen, P.; Peura, P.; Vidgen, M. Relative Pharmacokinetics of Three Oral 400 mg Ibuprofen Dosage Forms in Healthy Volunteers. Int. J. Clin. Pharmacol. Ther. Toxicol. **1991**, *29* (10), 381–385.
9. Perry, C.M.; Noble, S. Saquinavir Softgel Capsule Formulation. Drugs **1988**, *55* (3), 461–486.
10. Kovarik, J.M.; Mueller, E.A.; Van Bree, J.B.; Tetzloff, W.; Kutz, K. Reduced Inter- and Intraindividual Variability in Cyclosporine Pharmacokinetics from a Microemulsion Formulation. J. Pharm. Sci. **1994**, *83* (3), 444–446.
11. Trull, A.; Tan, K.K.C.; Tan, L.; Alexander, G.J.M.; Jamieson, N.V. Absorption of Cyclosporin from Conventional and New Microemulsion Oral Formulations in Liver Transplant Recipients with External Biliary Diversion. Br. J. Clin. Pharmacol. **1995**, *39*, 627–631.
12. Benet, L.Z.; Wacher, V.J. Use of Essential Oils to Increase Bioavailability of Orally Administered Pharmaceutical Compounds. US Patent 6,121,234, Sept 19, 2000.
13. Lacy, J.E.; Embleton J.K.; Perry E.A. Delivery Systems for Hydrophobic Drugs. US Patent 6,096,338, Aug 1, 2000.
14. Wacher, V.J.; Benet, L.Z. Propyl Gallate to Increase Bioavailability of Orally Administered Pharmaceutical Compounds. US Patent 5,962,522, Oct 5, 1999.
15. Makino, H.; Hakamada, I.; Yamada, O. Solvent System to be Enclosed in Capsules. US Patent 5,912,011, June 15, 1999.
16. Rinaldi, M.A.; Saxena, S.J.; Tutschek, P.C. Softgel Formulation Containing Retinol. US Patent 5,891,470, April 6, 1999.
17. Adesunloye, A.T.; Stach, P.E. Filled Gelatin Capsules. US Patent 5,874,106, Feb 23, 1999.

18. Bayless, R.E.; Laba, D.; Reynolds, W. Polyoxyalkylene Glycol Gelatin Capsule Fill Formulations Comprising Crosslinked Carboxylic Copolymers. US Patent 5,885,671, March 23, 1999.
19. Punto, L.; Potini, C.; Gould, E. Topical Application Emulsions. US Patent 5,587,149, Dec 24, 1996.
20. Lambrechts, J. Shampoo Conditioner and Softgel Filled Therewith. US Patent 5,573,756, Nov 12, 1996.
21. Morton, F.S.S.; Shelley, R.S.; Patel, M.S. Enhanced Solubility Pharmaceutical Solutions. US Patent 5,376,688, Dec 27, 1994.
22. Yamamoto, T.; Yagyu, M. Appearance Inspecting Device for Solid Formulation. US Patent 6,108,030, Aug 22, 2000.
23. Schurig, G.A.; Bezaire, B.; Ratko, B.; Baker, L.A.; Mikalian, R. Method for Striping or Marbleizing Capsules. US Patent 6,022,499, Feb 8, 2000.
24. Schmidt, W. Method for the Purification and Recovery of Waste Gelatin Using Diafilters. US Patent 5,945,001, Aug 31, 1999.
25. Bierdel-Willkommen, E.; Sambale, C.; Hahnlein, W. Soft Gelatin Capsules. US Patent 5,916,591, June 29, 1999.
26. Julius, K.; Bagusche, C. Method and Apparatus for Sorting Capsules. US Patent 5,819,953, Oct 13, 1998.
27. Rowe, D. Method and Apparatus for Forming Soft Gelatin Capsules Containing Particulate Material. US Patent 5,740,660, April 21, 1998.
28. Stroud, N.S.; Walker, D.J.; Garnett, K.R.; Burnett, A.J.; Wood, A.J. Encapsulation Apparatus and Process. US Patent 5,735,105, April 7, 1998.
29. Steele, D.; Dietel, G. Softgel Manufacturing Process. US Patent 5,200,191, April 6, 1993.
30. Morton, F.S.S.; Duque, P.P.; Chiprich, T.B.; Stroud, N.S. Methods for Preparing Gelatin Capsules Containing Fragrances. US Patent 6,099,858, Aug 8, 2000.
31. Hoy, M.R. Multiphase Soft Gelatin Dosage Form. US Patent 6,024,980, Feb 15, 2000.
32. Brox, W.; Meinzer, A.; Zande, H. Soft Gelatin Capsule Manufacture. US Patent 5,985,321, Nov 16, 1999.
33. Cody, S.L.; Devlin, B.T.; Dubek, J.; Hoy, M.R. Fill Material for Soft Gelatin Pharmaceutical Dosage Form. US Patent 5,919,481, July 6, 1999.
34. Hutchinson, K.G.; Garnett, K.R.; Fischer, G.; Page, N.S. Soft Gelatin Capsule Shell Compositions. US Patent 5,817,323, Oct 6, 1998.
35. Stone, D.D. Graphically Impressed Softgel and Method for Making Same. US Patent 5,827,535, Oct 27, 1998.
36. Hutchison, K.G.; Garnett, K.R. Method of Preparing a Water-Based Beverage. US Patent 5,681,606, Oct 28, 1997.
37. Tanner, K.; Orange, K. Tamper Evident Pharmaceutical Dosage Form. US Patent 5,624,681, April 29, 1997.
38. Chiprich, T.B.; Hoylman, M.T.; Stroud, N.S. Capsule Shell Formulation to Produce Brittle Capsules. US Patent 5,641,217, March 25, 1997.
39. Stroud, N.S. High Amylose Starch Substituted Gelatin Capsules. US Patent 5,554,385, Sept 10, 1996.
40. Brox, W.; Block, P.; Schafer, R. Printed Shaped Bodies and Sheets Containing Gelatin. US Patent 5,529,767, June 25, 1996.